METABOLIC DISTURBANCES IN DISSEMINATED NEOPLASTIC DISEASE*†

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METABOLISM has been defined as tissue change and as such it is a term which can be applied to all the chemical functions of a cell. It is not my intention to review the metabolism of a cancer cell but rather to discuss certain biochemical alterations, occurring in the course of disseminated cancer, which lead to clinical symptoms and signs. My objectives are to indicate the broad scope of these disturbances and to illustrate how some can be managed. Points concerning management are offered in the belief that a physician discharges his fullest duty to his patient only when he undertakes to alleviate his patient's problems, regardless of the fact that a particular situation may be ultimately fatal.

A general classification is shown in Table I. The presence of tumor in an organ system may obviously lead to deranged function by interfering with the normal physiological processes of that system. Metabolic disturbances may arise also as a result of the action of substances produced by tumors or as a result of the rapid anabolism and catabolism of tumor tissue. Finally, owing to the more aggressive therapeutic approach to the problems of disseminated cancer, metabolic disturbances may result from treatment.

Some of the disturbances which result from disruption of organ systems by tumor are outlined in Table II. *Hypoproteinemia* and *defective hepatic glycogenesis* have been described in patients with gastric carcinoma and restoration of plasma protein levels to normal was found not to occur despite establishment of a positive nitrogen balance.[1] The mechanisms underlying these changes are unknown.

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TABLE I.—METABOLIC DISTURBANCES IN NEOPLASTIC DISEASE

1. Those related to the presence of tumor in certain organ systems.
2. Those produced by substances which have been elaborated by tumors.
3. Those related to the rapid anabolism and catabolism of tumor tissue.
4. Those related to the treatment of neoplastic disease.

TABLE II.—SOME DISTURBANCES RELATED TO THE PRESENCE OF TUMORS IN ORGAN SYSTEMS

GI tract: Hypoproteinemia; hypokalemic alkalosis
Liver: Liver coma; hypoglycemia; ammonia intoxication
Lung: Anoxemia; respiratory acidosis
Skeleton: Hypercalcemia with hyper- or hypophosphatemia
GU tract: Renal acidosis; nephrotic syndrome
CNS: Respiratory acid-base disturbances; hypernatremia
Endocrine: Adrenal insufficiency; diabetes insipidus
General: "Third-space" effects; "Dissolution syndrome"

Whether the tumor disrupts some metabolic activity of the stomach thus causing hypoproteinemia or whether these effects are mediated through altered liver or adrenal function or through some other mechanism cannot be stated. The *electrolyte disturbances* of disseminated cancer involving the gastrointestinal tract are most commonly the hypochloremic, hypopotassemic alkalosis of high intestinal obstruction and the metabolic acidosis of excessive small intestinal losses. Intraperitoneal seeding of tumor may lead to ascites formation with expansion of the extracellular space into a sequestered fluid collection, a so-called "*third space*".[2] We have observed a patient with vesico-rectal fistula who developed *hyperchloremic acidosis* which appeared to be due to pooling of urine in the sigmoid in a fashion similar to what may be seen in ureterosigmoidostomy.[3, 4]

Hypoglycemia has been observed as a feature both of primary and metastatic disease of the liver and with malignant spindle cell tumors.[5, 6] A recent report[7] described a patient who was brought into the hospital in coma and hypoglycemia was suspected when the cerebrospinal fluid

sugar was found to be low. Hypoglycemia was confirmed and was found to be responsive but later unresponsive to dextrose infusions. At postmortem examination an extensive hepatoma was discovered. A low cerebrospinal fluid sugar may not necessarily indicate hypoglycemia but rather may be a sign of meningeal metastases.[8] This may initially cause confusion with more well-known causes of lowered cerebrospinal fluid sugar such as bacterial and tuberculous meningitis.

Coma in patients with liver failure may be due to an *elevation of blood ammonia* and such patients have been found to have *respiratory alkalosis* in the early phases of ammonia intoxication.[9] Treatment measures include oral antibiotics,[10] frequent enemas to reduce ammonia production, sodium glutamate, and more recently arginine, by vein to decrease the circulating ammonia.[11, 12]

The phenomenon of *hypercalcemia* may result when the rate of growth of tumor in bone is such that calcium enters the blood stream at a rate which exceeds the ability of the kidneys to clear it.[13, 14] Rarely hypercalcemia may occur without detectable bone disease.[15] One example of this will be considered shortly.

Renal failure with metabolic acidosis is usually encountered in patients with pelvic tumors obstructing both ureters. Although the immediate management is similar to the treatment of renal acidosis from any cause, relief of the underlying ureteral obstruction is essential and can be achieved in some patients by roentgen therapy to the pelvic tumor whereas nephrostomy may have to be done in others. In some instances intra-arterial nitrogen mustard[16] has been used to cause regression of pelvic tumors. An intra-arterial catheter is introduced in a retrograde fashion into the lower abdominal aorta via the femoral artery and the appropriate dose of nitrogen mustard is delivered through the catheter. This technique permits the maximum effect to be delivered to the area under treatment.

Rarely, the *nephrotic syndrome* may be encountered as a result of renal amyloidosis seen at times in association with Hodgkin's disease and multiple myeloma.[17, 18] The nephrotic syndrome may occur also as a result of bilateral renal vein thrombosis[19, 20] secondary to multiple thromboses and, although no reports have been encountered by us, the syndrome might conceivably result from compression of the renal veins by the tumor.

The various electrolyte abnormalities listed under the central nerv-

ous system and pulmonary system (Table II) are well established. In addition to the *respiratory acid-base changes* which may be seen in central nervous system lesions, *hypernatremia* has been described in such patients (without evidence of diabetes insipidus) and renal wastage of salt has also been observed.[21] Extensive intrapulmonary metastases may impair exchange of respiratory gases with resultant *alveolar respiratory insufficiency*.[22] We have observed a patient who had reticulum cell sarcoma of the lungs and *respiratory acidosis* which was temporarily relieved after the administration of nitrogen mustard.[23]

Involvement of endocrine organs may lead to insufficiency of the organ concerned although the mere presence of tumor does not necessarily indicate that an endocrine gland will be functionally inadequate. Although carcinomas (particularly of the lung) often metastasize to the adrenals, actual clinical symptomatology of *adrenal failure* is difficult to distinguish from the total picture of deterioration. The use of adrenal steroids as replacement therapy is often tried but with little success. *Diabetes insipidus* has been described as a result of pituitary metastases but this is a rare phenomenon. In a recent report only six necropsy-proven cases could be found in the literature over a period of 30 years.[24]

Some terminally ill patients demonstrate general electrolyte abnormalities which appear to be indicative of impending dissolution. This "*dissolution syndrome*" is usually characterized in our experience by a falling serum sodium, a rising serum potassium and over-expansion of the extracellular space, and is presumably related to altered cell membrane permeability. Rubin and co-workers[25] reported that in a group of 78 seriously ill patients the measured plasma osmolality exceeded by 40-125 milliosmols per kilogram of water the calculated value. Ninety-eight per cent of these patients died within two weeks after the finding of hyperosmolality. The changes are non-specific, however, and may be seen in any long-standing illness near its termination.

Thus far we have considered briefly the numerous metabolic disturbances which may arise as a consequence of the presence of tumor in certain organs. Figure 1 illustrates the management of one such disturbance, hypercalcemia, in a patient with lymphosarcoma. At a time when this patient was comatose owing to hypercalcemia, she was given nitrogen mustard 0.3 mg./kg. intravenously. There followed

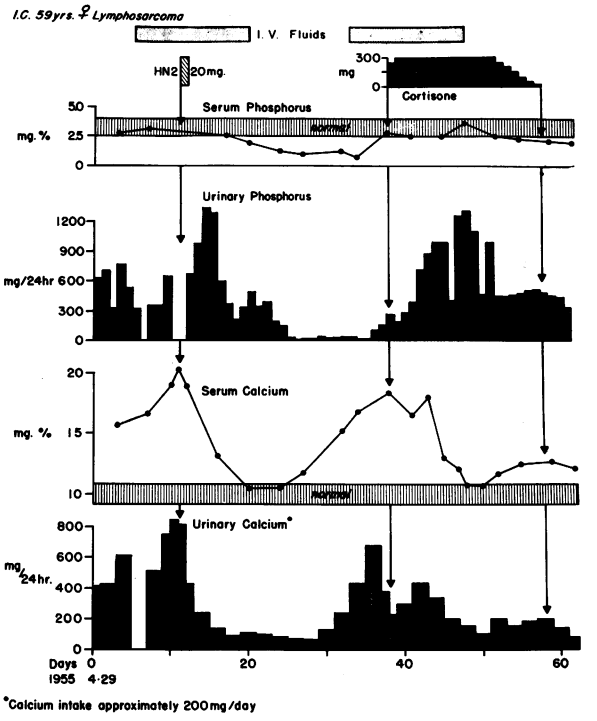

Figure 1.—Calcium and phosphorus levels in the serum and urine in a patient with lymphosarcoma treated with nitrogen mustard and cortisone.

a rapid decrease in the serum and urinary calcium levels to normal. The patient gradually regained consciousness and improved sufficiently to be up in a wheelchair and to eat a regular diet again. The hypercalcemia soon recurred, however, and on this second occasion reversal of these changes was accomplished by treatment with cortisone. The hypophosphatemia, hypercalcemia and hypercalcuria raised the possibility of an independent hyperparathyroidism but a subsequent postmortem examination revealed normal parathyroid glands. Although serum phosphorus levels have been reported to be slightly higher than normal in patients with disseminated bone cancer,[13] in our recent experience the level of phosphorus in the blood may be high or low in such situations and has not been of much help in differentiating hypercalcemia of malignant bone disease from that due to other causes. An additional finding of interest was that bone marrow invasion by tumor could not

TABLE III.

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July 1953: Radical hysterectomy for carcinoma of the cervix.
August 1953: Calcific shadow right kidney; right hydronephrosis.
August 1953-July 1955: Recurrent pyelonephritis.
July 1955: Admitted for pyelonephritis and polyuria.

Blood sugar 294 mg.%	*Skeletal survey:* demineralization
Serum calcium 15.5 mg.%	*Serum protein* 9.0 gm.% *Albumin* 4.5 gm.%
Serum phosphorus 2.7 mg.%	*Cephalin flocculation* ++++ *BSP* 30%
Urinary calcium 176 mg./24 hrs.	*Hemoglobin* 7.6 gm.%
Alkaline phosphatase 11.7 Bodansky Units	*Marrow:* hypocellular *BUN* 18.2 mg.%

Differential diagnosis
Hyperparathyroidism
Osseous metastases with hypercalcemia
Myeloma with hypercalcemia
Sarcoidosis with hypercalcemia

be demonstrated either by roentgen survey of the skeleton, by bone marrow aspirations during life or by examination of the bones at autopsy. Bone metastases can be demonstrated in the great majority of instances of hypercalcemia in malignant disease but there are a few instances in which they cannot.[15] The mechanism of such hypercalcemia remains unknown, although it has been postulated that some tumors may secrete a bone-resorbing substance.[26] Although nitrogen mustard and cortisone have been used most often in the management of hypercalcemia in disseminated cancer, a new antimetabolite, 6-diazo-5-oxo-L-norleucine (DON) has also proved useful in the treatment of this complication.[27]

The metabolic complexities which can arise in patients with cancer are outlined in Table III which summarizes the pertinent clinical information in a patient with carcinoma of the cervix. Although definite dissemination of this patient's disease could not be demonstrated conclusively, such was suspected because of anemia, hepatomegaly, abnormal liver function and hydronephrosis. When the polyuria, which was attributed to diabetes mellitus, did not fully subside with insulin administration other causes for polyuria were investigated. Findings compatible with hyperparathyroidism were noted but in addition the other laboratory data made tenable any one of the four diagnoses listed. The

TABLE IV.—PRIMARY SITES OF FUNCTIONING TUMORS AND SOME DISTURBANCES WHICH THEY PRODUCE

Pituitary	Cushing's
Thyroid	Hyperthyroidism
Parathyroids	Hyperparathyroidism
Adrenals	Cushing's; pheochromocytoma; aldosteronism
Pancreas	Hyperinsulinism
Gonads	Masculinizing and feminizing syndromes
Miscellaneous	Malignant carcinoid; dysproteinemias

possibility of osseous metastases could not be substantiated by bone marrow aspiration, and the skeletal survey revealed minimal but generalized demineralization rather than lytic lesions. The anemia was regarded as probably secondary to long-standing renal disease and chronic infection although anemia has been noted in patients with hyperparathyroidism with extensive osteitis fibrosa.[28] Inasmuch as there was no Bence-Jones proteinuria and no myeloma cells were noted on marrow aspiration the possibility of multiple myeloma was excluded. An electrophoretic study of the serum proteins revealed an increase in a_2 globulin but no spike configuration of gamma globulin typical of myeloma protein. The clinical and laboratory findings were compatible with sarcoidosis but there was no peripheral or hilar lymphadenopathy and no skin or bone lesions suggestive of sarcoidosis. The patient was accordingly explored and a parathyroid adenoma was found in the left retroclavicular region. She recovered and remained well until a year later when she succumbed to widespread cancer. This case serves as a reminder that although metabolic disturbances may arise as a consequence of disseminated cancer, coincidental but unrelated metabolic diseases may occur to confound the clinician.

Some of the disturbances of neoplasms of endocrine organs produced by virtue of the hormonal substances elaborated are shown in Table IV. By far the great majority of these disturbances are caused by hyperfunctioning adenomas but there are, however, a small number of instances of disseminated hyperfunctioning malignant tumors of endocrine origin. *Cushing's syndrome* may result from metastatic carcinoma of the basophil cells of the pituitary[29] but this is rare compared

to adrenocortical carcinoma as a cause of this disorder. When Cushing's syndrome occurs as a result of metastatic carcinoma, there is little to offer the patient, although recent studies with amphenone B,[30] which apparently specifically inhibits the synthesis of biologically active 17-hydroxycorticoids, hold promise for treatment of such patients in the future. Patients with *hyperthyroidism* due to cancer of the thyroid with functioning metastases can be restored to a euthyroid state by treatment with thiouracil and radioiodine.[31] Carcinomas of the parathyroids are rare, only one case in more than 100 cases of *hyperparathyroidism* having been observed by Black at the Mayo Clinic.[32] Treatment consists in removing as much hyperfunctioning tissue as possible if the disease is locally extensive. If disseminated, there is no known effective measure, although a parahormone inhibitor would be of theoretical value if such existed.

Functioning malignant *pheochromocytomas* have been reported[33] and Regitine offers a possible approach to therapy in controlling the hypertension of disseminated tumors of this origin. The syndrome of primary aldosteronism recently described by Conn[34, 35] is usually associated with adrenocortical adenoma but has also been found to occur with adrenal cortical carcinoma.[36] The first surgically proven case of *hyperinsulinism* was a carcinoma of the islet cells with liver metastases.[37] In a review by Crain and Thorn[38] about 10 per cent of 258 cases of hyperinsulinism were due to metastatic carcinoma of the islet cells. Although alloxan is of theoretical value in such cases, practically speaking it has proved to be too toxic for clinical use.[6, 38] *Masculinizing* and *feminizing syndromes* are well-known examples of disturbances produced by substances elaborated by tumors. Although such syndromes are frequently adrenal in origin, gonadal causes must always be considered.[39, 40]

One of the most exciting chapters in the field of hyperfunctioning tumors has been written recently with the description of a clinical syndrome due to *malignant carcinoid*.[41, 42] Apparently most cases have liver metastases although these are said to be non-essential for the production of the syndrome. The clinical findings consist of vasomotor disturbances (usually cyanosis and flushing), chronic diarrhea, asthmatic-like respiratory symptoms and valvular disease of the right side of the heart. These changes are thought to result from serotonin which is secreted by the tumor. Sjoerdsma, Weissbach and Uden-

TABLE V.—SOME DISTURBANCES RELATED TO THE RAPID ANABOLISM AND CATABOLISM OF TUMOR TISSUE

Lymphomas and leukemias	Uric acid lithiasis
Leukemia	Elevated basal metabolism
General	Weight loss, malnutrition, fever

friend[41] found that whereas normally only about one per cent of dietary tryptophan is metabolized to serotonin, in patients with malignant carcinoid as much as 60 per cent of ingested tryptophan is converted to serotonin, thus demonstrating an abnormal diversion presumably as a result of the metabolic activity of the tumor.

The *dysproteinemias* include the increasingly complex protein disturbances of multiple myeloma[43] as well as cryo- and macroglobulinemia.[44, 45] Some of these proteins may lead to disturbances such as bleeding, purpura, and Raynaud's phenomenon.

Disturbances due to *rapid turnover of tumor tissue* are summarized in Table V. Since rate of change is important in the production of some of these disturbances it is not unexpected that they occur chiefly in the lymphomatous diseases, where marked changes in tumor growth may occur spontaneously (or as a result of treatment) in relatively short periods of time. *Uric acid lithiasis*, although more often seen as a complication of therapy[46, 47] may occur spontaneously. There are no known effective measures in treatment other than to enhance the solubility of uric acid by making the urine alkaline and to ensure that the patient's fluid intake and output is plentiful. Ureteral irrigation may occasionally be of help when there has been extensive crystallization in the ureters. Since uric acid may be dialyzed, the use of an artificial kidney should be considered in situations of renal shutdown due to uric acid lithiasis. It has been suggested that uricosuric agents be used prior to radiotherapy in patients with hyperuricemia.[47] However, we feel the use of these agents should be avoided, since in the majority of instances the problem is not one of diminished renal clearance, but one of a marked increase in uric acid excretion accompanied by uric acid crystallization in the kidneys and ureters. One possible exception is their cautious use in pre-treatment periods if the elevated blood

TABLE VI.—TREATMENT OF NEOPLASTIC DISEASE AND SOME DISTURBANCES RELATED TO IT

Surgery:	Dumping syndrome (gastrectomy)
	Hypoparathyroidism (radical neck dissection)
	Myxedema (hypophysectomy or radical neck dissection)
	Diabetes insipidus (hypophysectomy)
	Adrenal insufficiency (hypophysectomy or adrenalectomy)
	Hyperchloremic acidosis (ureterosigmoidostomy)
	Diabetes mellitus (total pancreatectomy)
Radiation therapy and Chemotherapy:	Electrolyte abnormalities
	Uric acid lithiasis
Sex Steroids:	Hypercalcemia
	Salt retention with edema
Adrenal Steroids:	Cushing's
	Steroid diabetes
	Hypokalemia

uric acid is associated with a low urinary uric acid and measures such as fluids and alkalinization have failed to correct the hyperuricemia.

The *elevated basal metabolism* seen in some patients with acute leukemia has been recognized for many years. The mechanism has been related to increased oxygen utilization by leukemic cells by some investigators while others have felt this to be an inadequate explanation and have related the change to a marked increase in nitrogen catabolism.[48] Whatever the exact cause, the elevated metabolic rate, fever and tachycardia return to normal when a remission is induced. The *weight loss and malnutrition* of disseminated cancer are associated with a negative nitrogen balance but exactly what triggers the series of changes leading to these abnormalities is not clear. Their inclusion under the general topic of anabolism and catabolism is not meant to imply that they are due to rapid turnover of tumor tissue per se but rather to mean that weight loss and malnutrition are complex metabolic disturbances which may result from cancer growth even though specific disruption of a vital organ system cannot be demonstrated.[49] It has been reported[50] that once a negative nitrogen balance is established it is very difficult to re-establish a positive nitrogen balance since in these patients nitrogen losses are further stimulated by increasing the intake. This

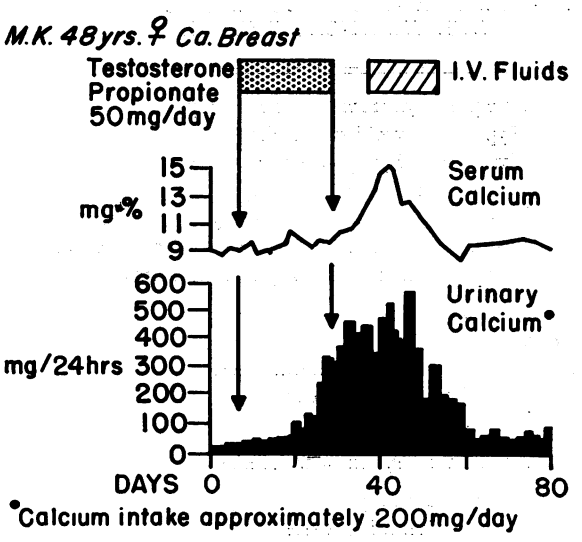

Figure 2.—Serum and urinary calcium data in a patient with metastatic mammary carcinoma under treatment with testosterone propionate. (Reprinted, by permission, from Myers, W. P. L. Medical Clinics of North America 40:871-885, 1956, ref. 14.)

is true up to a point beyond which retention may be achieved but the intakes required are usually far in excess of what is necessary to achieve a positive nitrogen balance in normals.[50]

The final category of disturbances, namely those related to the treatment of disseminated cancer, is outlined in Table VI. Various surgical procedures including gastrectomy, hypophysectomy, adrenalectomy and ureterosigmoidostomy may lead, respectively, to the *dumping syndrome*, *diabetes insipidus*, *myxedema*, *adrenal insufficiency* and *hyperchloremic acidosis*. The management of these situations has been extensively reviewed[3, 4, 51-53] and will not be reviewed here. It need hardly be emphasized, however, that the management of these metabolic disturbances should be thoroughly understood when these surgical procedures are employed. *Myxedema* and *hypoparathyroidism* following radical neck dissections for thyroid carcinoma pose no special problems in management although we have encountered a few hypoparathyroid patients with hypercalcemia secondary to *over-treatment with vitamin D*. The *diabetes mellitus* following total pancreatectomy is usually mild and readily controlled.

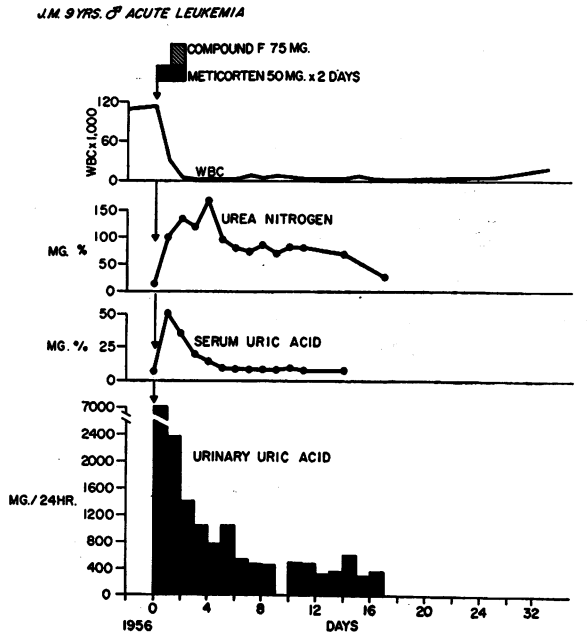

Figure 3.—Data on serum and urinary uric acid levels in a 9 year old boy with acute leukemia under treatment with adrenal steroids.

The use of drugs and radiation therapy in the treatment of disseminated cancer may induce a variety of disturbances including *electrolyte disorders, hyperuricemia,* and *functional abnormalities of the liver.* The serum and urinary uric acid changes induced by therapy in a young boy with acute leukemia are illustrated in Figure 2. After 50 mg. of Meticorten had been administered over a period of 12 hours, marked hyperuricemia developed accompanied by a huge output of uric acid in the urine. In addition there was a rise in the blood urea nitrogen to levels above 150 mg. per cent. Although renal shutdown secondary to uric acid lithiasis did not occur in this patient, it may occur following both chemotherapy and radiation therapy[46, 47] and hence represents a problem to be reckoned with, particularly in the treatment of lymphomas and leukemias. Patients undergoing treatment with radiation are also prone to develop a *negative nitrogen balance*[50] and weight loss and malnutrition may occur as a consequence.

In addition to *salt retention with edema* formation, *hypercalcemia*

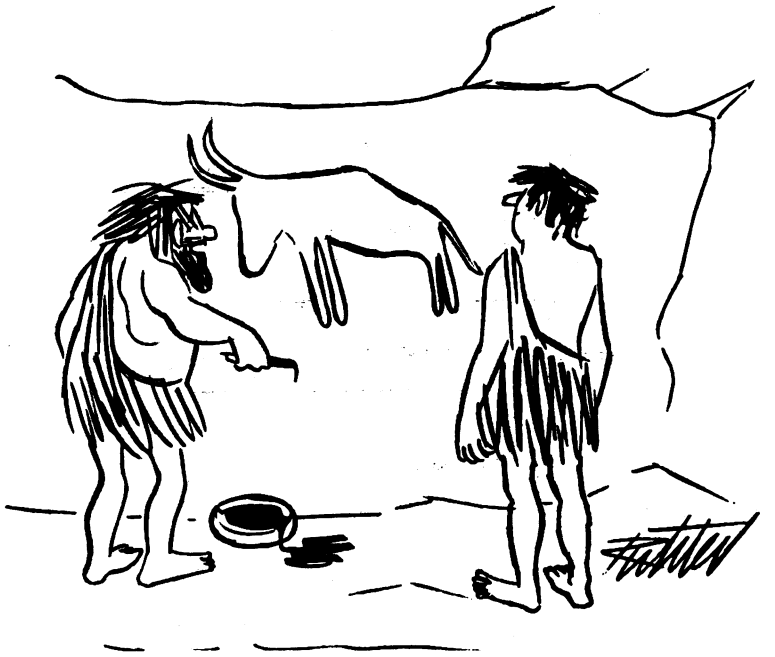

Figure 4.—*"Well, there you are, young fellow. I've taught you everything I know."*—Drawing by Richter.

may result from the use of sex steroids.[54-56] This metabolic hazard may arise with both androgen and estrogen therapy and its occurrence with the former is illustrated in Figure 3. The rising urinary calcium, during a course of testosterone therapy for metastatic breast cancer, afforded an excellent guide to impending hypercalcemia and the steroid was stopped at a time when the patient was still normocalcemic. The serum calcium subsequently reached a peak of 15 mg. per cent two weeks after cessation of treatment apparently as a result of the delayed effects of the intramuscular therapy. Since hypercalcemia may be fatal it is important to be mindful of its possible occurrence during the treatment of disseminated breast cancer.

Cushing's syndrome is usually seen only with the prolonged use of adrenal steroids and yet the malignant disease under treatment often demands continuation of these hormones. Some control may be achieved by reduction in dosage and the use of androgens concomitantly for

their anabolic effect should be considered. "*Steroid diabetes*", which is characterized by insulin unresponsiveness, diminution in glycosuria with fasting and a negative nitrogen balance,[57] occurs infrequently but is nevertheless of sufficient importance to be watched for in all patients undergoing treatment with adrenal steroids. This is particularly true of those with a positive family history for diabetes. *Potassium deficiencies* are frequent with prolonged adrenal steroid therapy and supplementary potassium is usually necessary.

Figure 4 in all probability summarizes the content of this paper. I can only hope that the exposition of the material is as clear.

Summary: A review of some of the metabolic disturbances in disseminated cancer has been presented together with considerations regarding management.

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